REMARKS

Claims 1, 4-6, 10-15, 18-38, 43-45, and 48-55 remain pending herein. Claims 7-8, 16-17, 40-42, and 46-47 are hereby canceled without prejudice or waiver of the right to pursue the subject matter of said claims in this or another application. Claims 1, 10, 43, 45, and 48 have been amended. New claim 55 has been added. All other claims remain the same. Reconsideration of the claims as pending is respectfully requested.

Prior to addressing the merits of the Office Action, Applicants acknowledge with appreciation the careful attention examiner has paid to this application. Applicants also acknowledge with appreciation the courtesies extended to Dr. Glenn Meyer and the undersigned during the interview of February 23, 2004 during which the merits of the Office Action, the text of a proposed amendment, earlier filed declarations, and the prior art of record were discussed. It was agreed that a narrowed scope defining the COX-II inhibitor might be considered for allowance, especially if the compound scope of the independent claims were limited to that of claims 40 or 49. Examiner indicated that submission of additional data demonstrating synergy between other combinations of a selective or specific COX-II inhibitor and a muscle relaxant might be sufficient to support allowance of the more broadly claimed scope originally filed in claim 1. Examiner requested additional explanation regarding the data filed in prior declarations be included with the response.

Accordingly, Applicants have amended the claims to more narrowly define the scope of selective or specific COX-II inhibitor compounds as defined in original claim 40. Applicants have also provided further discussion regarding the data presented in earlier filed declarations that establish statistically significant therapeutic synergy for coadministration of a selective or specific COX-II inhibitor and a muscle relaxant. During the pendency of this application, Applicants intend to file additional experimental data under a Rule 1.132 Declaration for other combinations of a selective or specific COX-II inhibitor and a muscle relaxant.

Examiner requested that the broadest claims be limited to specific groups of compounds. In particular, Examiner pointed to claims 40 and 49 as being enabled by the specification (page 5, last para. of the Office Action). Accordingly, the independent claims have been amended to recite specific COX-II inhibitors and muscle relaxants.

Applicants note that Examiner incorrectly identifies the combination of diclofenac and pridinol, of the declarations, as being part of the claimed combination. That combination is used

as a control in the study. Diclofenac is an NSAID, not a selective or specific COX-II receptor inhibitor.

Claims 1, 4, 5, 8, 10, 13-14, 17-38, and 40 stand rejected under 37 C.F.R. §112, 1st para. for allegedly containing new subject matter. The phrases, "wherein the inhibitor binds COX-II receptors selectively over COX-I receptors or binds COX-II receptors specifically" and "providing an additive or synergistic therapeutic effect", are particularly identified with regard to claims 1, 10, and 40. The phrases, "release at a faster rate than the muscle" and "released at a slower", are particularly identified with regard to claims 12, 29, 34, 36 and 52-53. The addition of chemical names, "NS-398, DUP-697, SC-57666 and T-614", is particularly identified with regard to claims 8, 17 and 40. Insofar as it may apply to the present claims, the rejection is respectfully traversed. As discussed during the above-mentioned interview, Applicants submit that the claims are fully supported by the specification as originally filed.

Claims 8, 17, and 40 have been canceled.

The specification as originally filed (page 7, lines 18-20) includes the phrase, "COX-II inhibitors useful in the present invention include those compounds that are selective for COX-II receptor inhibition over COX-I inhibition or that are specific receptor inhibitors."

The specification as originally filed (page 5, lines 24-25) includes the phrase, "Depending upon the particular combination of COX-II inhibitor and muscle relaxant used, an improved (enhanced), additive or synergistic therapeutic effect will be observed." Moreover, the specification (page 29, line 26 to page 30, line 9) includes the definition of the terms "improved", "additive" and "synergistic" therapeutic effect. Even so, during the interview, Examiner suggested that the requirement of a synergistic therapeutic effect be removed from the claims in order to overcome this aspect of the rejection. Therefore, the claims have been amended to remove such limitation.

With regard to claim 12, the phrases, "release at a faster rate than the muscle" and "released at a slower", describe the general performance of two embodiments of the pharmaceutical dosage form when exposed to an environment of use. The subject matter of claims 12, 29, 34, 36 and 52-53 is well supported in the specification as originally filed. Example 1 provides a dosage form wherein both drugs are present in immediate release form, which the artisan will recognize as releasing drug rapidly; therefore, the drugs are released "at approximately the same rate". The dosage forms of Examples 4-9 and 12 also provide this type

of substantially similar release rate. Examples 2 and 11 provide dosage forms that release the muscle relaxant at a sustained rate, which the artisan will recognize as releasing drug slowly, and the COX-II inhibitor is released immediately; therefore, the "COX-II inhibitor is released at a faster rate than the muscle relaxant." Examples 3 and 13 provide dosage forms that provide a controlled release, which the artisan will recognize as a slow release, of the COX-II inhibitor and an immediate release of the muscle relaxant; therefore, the "COX-II inhibitor is released at a slower rate than the muscle relaxant." During the interview, Examiner requested that the different combination of release profiles be placed in separate claims. Therefore, new claim 55, specifying that the drugs are released according to different release profiles, has been added. As noted above, the specification includes exemplary formulations wherein the drugs are released according to different release profiles. With regard to claims 29, 34, 36 and 52-53, Applicants note that said claims do not include the objectionable language of claim 12.

The chemical names for NS-398, DUP-697, SC-57666 and T-614 are well known in the art. Applicant has filed herewith a Supplemental Information Disclosure Statement including references that specifically correlate the above-mentioned development drug codes (these are not trade names) with their corresponding chemical names: NS-398 (abstract of *Gen. Pharmacol.* (1993), 24(1), 105-110); DUP-697 (*J. Pharmacol. Exp. Ther.* (1990), 254(1), 180-187); T-614 (*Arnzneimittelforschung* (1992), 42(7), 945-50); SC-57666 (DIALOG™ database print-out).

Applicants respectfully submit that the rejection of claims 1, 4, 5, 8, 10, 13-14, 17-38, and 40 under 37 C.F.R. §112, 1st para. has been overcome and request that it be withdrawn.

Claims 1, 4, 5, 10, 13-14, and 18-38 stand rejected under 37 C.F.R. §112, 1st para. for scope of enablement. Examiner states that the phrases, "a COX-II inhibitor wherein the inhibitor binds COX-II receptors selectively over COX-I receptors or binds COX-II receptors specifically" and "a muscle relaxant" are seen to be merely functional language. Examiner contends that the breadth of claim scope in view of the specification would require an artisan to perform undue experimentation in practicing the invention as claimed. Examiner further contends that the art is highly unpredictable. Examiner states, "Hence, in the absence of fully recognizing the identity of the members [of the] genus herein, one of skill in the art is unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein." Insofar as it may apply to the present claims, Applicants

respectfully disagree. Applicants submit that the specification fully recognizes the identity of the members of the genus, especially in view of the prior art.

Claims 4-5 depend from and include the subject matter of independent claim 1, and claims 13-14 and 18-38 depend from and include the subject matter of independent claim 10. Claims 1 and 10 have been amended as requested by Examiner during the interview to include specific lists of the drugs commensurate in scope with claim 40. Even so, Applicants wish to enter the following remarks into the record.

Applicants submit that therapeutic compounds are very often identified (classified) by either their *in vivo* mechanism or the overall function (affect) that a therapeutic compound provides *in vivo*. For example, compounds are classified as anti-inflammatory (therapeutic effect), H1 receptor antagonist (*in vivo* mechanism), farnesyl protein transferase inhibitor (*in vivo* mechanism), antiotensin-converting enzyme inhibitor (*in vivo* mechanism), prostaglandin FP receptor agonist (*in vivo* mechanism), decongestant (therapeutic effect), prostaglandin synthesis inhibitor (*in vivo* mechanism), antibiotic (therapeutic effect), antihistamine (*in vivo* mechanism), antiparasitic (therapeutic effect), antiviral (therapeutic effect), local anesthetic (therapeutic effect), antifungal (therapeutic effect), amoebicidal (therapeutic effect), trichomonocidal (therapeutic effect), analgesic (therapeutic effect), anti-arthritic (therapeutic effect), anti-asthmatic (therapeutic effect), anticoagulant (therapeutic effect), anticonvulsant (therapeutic effect), antidepressant (therapeutic effect), antidiabetic (therapeutic effect), antineoplastic (therapeutic effect), anti-psychotic (therapeutic effect), HIV protease inhibitor (*in vivo* mechanism), neuroleptic (therapeutic effect), antihypertensive (therapeutic effect), hypnotic (therapeutic effect), sedative (therapeutic effect), anxiolytic energizer (therapeutic effect), antiparkinson agent (therapeutic effect), muscle relaxant (therapeutic effect), antimalarial (therapeutic effect), contraceptive (therapeutic effect), anti-hypoglycemic (therapeutic effect), antilipemic (therapeutic effect), ophthalmic (therapeutic effect), prokinetic agent (therapeutic effect), gastric acid secretion inhibitor (therapeutic effect), anti-ulcerant agent (therapeutic effect), anti-flatulent agent (therapeutic effect), anti-incontinence agent (therapeutic effect), insulin sensitivity enhancer (*in vivo* mechanism), opioid agonist (*iv vivo* mechanism), PDE3 inhibitor (*in vivo* mechanism), opioid antagonist (*in vivo* mechanism), NSAID (structural class of drug). Moreover, there are literally hundreds, if not thousands, of U.S. patents that have issued that identify drugs strictly functionally in the broadest independent claims, e.g. U.S. Patents No.

6,673,831, No. 6,669,955, No. 6,653,336, No. 6,610,682, No. 6,599,923, No. 6,528,511, No. 6,479,551, No. 6,475,494, No. 6,476,037, and No. 6,472,421, to name just a few of the more recent ones. Note, all of the cited patents issued after the dates of the cases cited by Examiner. Applicants have merely followed the common standards of patent practice.

Applicants submit that Examiner has not provided any evidence establishing the unpredictability in the specific art area being claimed, i.e. the combined administration of a specific or selective COX-II receptor inhibitor and a muscle relaxant. The text of Goodman & Gilman's, as cited by Examiner, is merely general language concerning potential possibilities when administering drug combinations to a subject. As evidence, Applicants submit that many U.S. patents have issued wherein the claims merely recite combinations of drugs according to the drugs' *in vivo* mechanism or *in vivo* therapeutic effect(s). Moreover, those patents have issued well after the publication of the Goodman & Gilman's reference.

Applicants submit that the above-mentioned phrases are clearly defined and have acquired a definite meaning in the art and compounds exhibiting these properties are well known and easily recognizable in the art. The Supplemental IDS includes the publication of Verburg et al. (*Am. J. Therapeut.* (2001), 8, 49-64), which specifically defines the terms selective receptor inhibitor and specific receptor inhibitor (see pages 56-57 in the section entitled "A note on selectivity versus specificity"). Of particular relevance, the artisan defines these terms based upon the behavior (function) of compounds in a range of therapeutic plasma levels. In addition, the patent references cited in the present application also use the same criteria for identifying selective or specific COX-II receptor inhibitors. In view of this, an artisan is easily capable of identifying a selective or specific COX-II receptor inhibitor.

Examiner contends that the specification does not define the scope of compounds. Applicants disagree. As previously noted, the specification as originally filed (pages 7-10) includes recitation of a large list of COX-II (selective or specific) inhibitors that are suitable for use according to the invention. As required by examiner, the list specifically names some of the COX-II inhibitors considered within the scope of the invention. Moreover, the subject application includes patent citations disclosing the names and structures of suitable COX-II inhibitors and methods of preparing them.

In view of the above, Applicants submit that the genus of the claimed invention is well defined even though that genus might continue to expand if scientists continue to identify new

specific or selective COX-II receptor inhibitors and new muscle relaxants. Accordingly, one of ordinary skill in the art can readily visualize or recognize the identity of the members of the genus especially since the criteria for identifying such compounds is well known and artisans that invent those compounds will classify them as such.

Applicants respectfully submit that the rejection of claims 1, 4, 5, 10, 13-14, and 18-38 under 37 C.F.R. §112, 1st para. has been overcome and request that it be withdrawn.

Claims 1 and 4-8 stand rejected under 35 U.S.C. §112, 2nd para. for allegedly adding new subject matter. Examiner states that the specification contains no working examples showing the synergistic therapeutic effect of the claimed drug composition. Examiner also contends that the combination of rofecoxib and pridinol in the specification and declaration fails and shows only an additive or less than additive effect, and that a synergistic effect is not demonstrated. Insofar as it may apply to the present claims, this rejection is traversed.

Claim 1 has been amended to remove the requirement of a synergistic therapeutic effect. Even so, Applicants submit that the working examples in the specification do in fact include the drug combination of rofecoxib and pridinol, which, as detailed in the specification and declarations of record, provides a synergistic therapeutic effect *in vivo*.

The specification as originally filed (page 5, lines 24-25) includes the phrase, "Depending upon the particular combination of COX-II inhibitor and muscle relaxant used, an improved (enhanced), additive or synergistic therapeutic effect will be observed." The specification (page 29, line 26 to page 30, line 9) also includes the definition of the terms "improved", "additive" and "synergistic" therapeutic effect.

Accordingly, Applicants submit that the rejection of claims 1 and 4-8 under 35 U.S.C. §112, 2nd para. has been overcome and request that it be withdrawn.

Claims 1, 4-8, 10-38 and 40-54 stand rejected under 37 C.F.R. §103(a) as being unpatentable over Burch et al. in view of Okada et al. (US 5,476,663). Insofar as it may apply to the present claims, this rejection is respectfully traversed.

As discussed during the interview and in earlier filed declarations, the combination of a specific or selective COX-II inhibitor (such as rofecoxib) and a muscle relaxant (such as pridinol) does indeed provide a synergistic therapeutic effect when administered to a subject. Burch et al. and its combination with Okada et al. do not suggest that a synergistic therapeutic effect will be observed when a COX-II inhibitor is co-administered with a muscle relaxant.

During the interview, Examiner requested that additional discussion regarding the experimental data described in the earlier filed Rule 1.132 declarations be discussed for reconsideration. The requested discussion follows.

Table 1: Mean contortions per 10 minutes in mice for the pridinol, diclofenac sodium, rofecoxib and the combinations of rofecoxib or diclofenac with pridinol are shown. The p value showing the level of statistical significance compared to appropriate control groups is in the far right column.

Pridinol			
Dose (mg/kg)	Mean	S.D.	
0.0 (Normal saline)	18.8	4.3	
0.32	22.5	3.9	
0.64	21.7	6.5	
1.28	19.3	6.3	
2.56	18.3	7.3	
Diclofenac Sodium			
Dose (mg/kg)	Mean	S.D.	P value from Control
0.0 (Normal saline)	18.8	4.3	
16	14.8	9.9	0.4568
32	10.8	5.6	0.5330
64	9.0	9.3	0.9275
Rofecoxib			
Dose (mg/kg)	Mean	S.D.	P value from Control
0.0 (1% CMC)	28.3	9.7	
16	9.6	5.6	0.0004
32	15.3	8.7	0.0864
64	18.9	10.2	0.6597
Diclofenac Plus Pridinol			
Dose (mg/kg)	Mean	S.D.	P value from Control
0.0 (Normal saline)	17.8	12.1	
16	13.0	8.4	0.4208
32	19.2	6.0	0.8308
64	16.5	5.9	0.8054
Rofecoxib Plus Pridinol			P value from Control
Dose (mg/kg)	Mean	S.D.	
0.0 (1% CMC)	40.8	8.9	
16	16.0	9.9	0.0001
32	24.1	7.9	0.0012
64	17.1	8.6	0.0001

Supporting experimental mouse studies were conducted to demonstrate the level of baseline pain relief which could be achieved with each pain reliever alone (rofecoxib and diclofenac) and the muscle relaxant, pridinol. Sub-therapeutic doses were demonstrated pridinol and were identified for the diclofenac sodium and rofecoxib and the p value showing no statistical evidence of efficacy can be observed in Table 1. Specifically, the control group is the placebo vehicle system and the p values ranged from 0.4568 to 0.9275 over the dosage levels studied for diclofenac sodium and 0.0004 to 0.6597 for rofecoxib. The low dosage group for the rofecoxib did show statistical evidence of some efficacy but was included to show symmetry of doses administered and the p values illustrate that the higher dosage groups are truly sub-therapeutic. The dosage groups using the combination of diclofenac or rofecoxib and pridinol are the last two groups of Table 1. These data demonstrate the remarkable statistical significance attained when the combination of rofecoxib, a COX II inhibitor is co-administered with pridinol, a muscle relaxant ($p=0.0012$ at 32 mg/kg and $p=0.0001$ at 64 mg/kg). Surprisingly, the use of diclofenac, a known NSAID, and pridinol, a muscle relaxant, do not demonstrate any observable benefit from co-administration of these agents together ($p=0.4208$ at 16 mg/kg, $p=0.8308$ at 32 mg/kg and $p=0.8054$ at 64 mg/kg). This surprising result documents the highly beneficial nature of the invention by demonstrating the combination of a COX II and muscle relaxant to yield an efficacious pain reliever is superior to either agent alone. The examiners demonstrated a clear working understanding of this synergistic effect between the COX II agent rofecoxib and the muscle relaxant pridinol relative to the NSAID diclofenac and the muscle relaxant pridinol.

Even in view of the data establishing a synergistic therapeutic effect, Applicants wish to enter the following remarks into the record.

Applicants agree with Examiner that the prior art (Burch et al.) does not expressly disclose a COX-II inhibitor, e.g. rofecoxib, in combination with a muscle relaxant, e.g. pridinol, in a pharmaceutical dosage form. Applicants also agree with Examiner that the discovery or expectation of synergistic analgesic effect is unexpected.

Applicants disagree, however, that Burch et al. suggest the combination of a COX-II inhibitor and a muscle relaxant. Burch et al. is specifically directed to the combination of an analgesic and a COX-II inhibitor, which is considered by Burch et al. to be another analgesic type of drug. In order for the Burch et al. reference to be relevant it would have to equate a muscle

relaxant to an analgesic.[1] However, it is well known that an analgesic and a muscle relaxant have different therapeutic indications and mechanisms of action. Accordingly, the disclosure of Burch et al. fails to suggest the combined administration of a COX-II inhibitor and a muscle relaxant.

It appears that examiner has improperly applied hindsight reconstruction in combining the disclosures of Burch et al. and Okada et al. Combination of the disclosures of Burch et al. and Okada et al. fails to suggest the invention as claimed. Applicants disagree that Okada et al. teaches that a muscle relaxant such as pridinol is useful in combination with analgesic and/or anti-inflammatory drugs (Col. 3, lines 13-28).

The disclosure of Okada et al. was discussed during the interview, and it was agreed that Okada et al. do not suggest the combined use of a COX-II inhibitor and a muscle relaxant. Okada et al. focus on a particular type of dosage form that is suitable for the administration of a single drug at a time. Pridinol is merely included among a laundry list of compounds that can be included in the dosage form of Okada et al. In fact, a thorough search of Okada et al. reveals that they fail to even suggest the simultaneous administration of two or more drugs with their dosage form. In each case, the drugs are administered individually. The only combinations they suggest or disclose are combinations of excipients, the inactive agents. Accordingly, while the combination of Burch et al. and Okada et al. might suggest a COX-II inhibitor from Burch et al. with an analgesic drug chosen from the list Okada et al., the combination would not suggest a COX-II inhibitor and a muscle relaxant. Burch et al. would not be motivated to include a muscle relaxant from Okada et al., since such a prophetic combination would not include the analgesic agent that Burch et al. specifically requires.

Applicants note, the courts have clearly established that mere recitation of Applicants' claimed elements within the text of a prior art reference is insufficient to establish obviousness. The prior art must also suggest the combination of those elements and the expectation of success in using the suggested combination as proposed to be claimed by an applicant. The prophetic combination of Burch et al. and Okada et al. fails to suggest such combination.

Applicants submit that even if the prophetic combination of Burch et al. and Okada et al., or any other prior art, did suggest the combined use of an analgesic and a muscle relaxant, the

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[1] An analgesic is a compound that reduces or eliminates pain by inhibiting certain receptors in the body. A muscle relaxant is a compound that relaxes skeletal muscles in the body by acting on the central nervous system to relieve the stiffness and discomfort caused by strains, sprains, or other injury to muscles.

claimed invention would still remain patentable over such a disclosure, as the claimed invention provides an unexpected improved therapeutic effect over the proposed prophetic or prior art combination. This is demonstrated in the declarations of record.

In finding the claimed invention to be *prima facie* obvious, Examiner states, "At least additive therapeutic effects would have been reasonably expected." Applicants disagree.

The second Supplemental Declaration includes data obtained from the *in vivo* study comparing a claimed combination (rofecoxib and pridinol) to a control combination (diclofenac and pridinol). All of the compounds were administered at sub-therapeutic levels to more clearly identify additive or synergistic therapeutic effects. The data for the treated animals were normalized against the data for the control animals in order to establish a relevant scale for comparison. The data demonstrate that the combination of rofecoxib and pridinol provides a synergistic effect, but the comparative combination of diclofenac (analgesic) and pridinol does not. It is particularly important to note that the control composition does not even provide an additive therapeutic effect as contended by Examiner should occur. Applicants submit that the claimed combination provides an unexpectedly enhanced analgesic therapeutic benefit. Accordingly, the claimed combination is not *prima facie* obvious and is therefore patentable over the art of record. The courts have clearly established that the finding of an unexpected advantage provides ample basis for overcoming a rejection of *prima facie* obviousness.

In view of the above, applicants submit that the rejection of claims 1, 4-8, 10-38 and 40-54 under 37 C.F.R.§103(a) has been overcome and request that it be withdrawn.

Entry of the amendments indicated thereon into the record is requested. In view of all the foregoing, Applicants respectfully submit that the pending claims are patentable over the art of record and in form for allowance. An early notice of allowance thereof is requested.

Respectfully submitted,

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